PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/165, 31/58, 9/00 — A2

(11) International Publication Number: **WO 00/35441**

(43) International Publication Date: 22 June 2000 (22.06.00)

(21) International Application Number: PCT/US99/30163

(22) International Filing Date: 17 December 1999 (17.12.99)

(30) Priority Data:
09/215,280 18 December 1998 (18.12.98) US

(71) Applicant: BAKER NORTON PHARMACEUTICALS, INC. [US/US]; 4400 Biscayne Boulevard, Miami, FL 33137 (US).

(72) Inventors: BLONDINO, Frank, E.; 6237 Rose Terrace, Plantation, FL 33317 (US). BRUCATO, Michael; 9801 N.W. 1st Avenue, Miami Shores, FL 33150 (US). BUENAFE, Maria, W.; 110 Southshore Drive #3–C, Miami Beach, FL 33141 (US). CAVANAUGH, Kelly, A.; 27421 SW, 154th Avenue, Homstead, FL 33032 (US).

(74) Agents: LEVI–MINZI, Simona, A. et al.; Baker Norton Pharmaceuticals, Inc., 4400 Biscayne Boulevard, Miami, FL 33137 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: PHARMACEUTICAL AEROSOL FORMULATIONS CONTAINING FLUOROALKANES, BUDESONIDE AND FORMOTEROL

(57) Abstract

Provided is a solution aerosol formulation adapted for use in a pressurized aerosol container. The aerosol formulation is formulated from a composition containing Budesonide, Formoterol at least one fluoroalkane propellant, and a cosolvent present in an amount that dissolves or solubilizes the Budesonide and Formoterol in the mixture of cosolvent and propellant.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

PHARMACEUTICAL AEROSOL FORMULATIONS CONTAINING FLUOROALKANES, BUDESONIDE AND FORMOTEROL

1. Field of the Invention.

The invention relates to pharmaceutical aerosol formulations containing Budesonide and Formoterol dissolved or solubilized in a fluoroalkane(s) and a cosolvent(s).

2. Background of the Invention.

Chlorohydrocarbon and chlorofluorocarbon propellants used in medical aerosol formulations are generally considered to be environmentally unfriendly. Therefore, these propellants have been largely replaced by hydrofluoroalkanes such as 1,1,1,2 tetrafluoroethane ("HFA-134a") and 1,1,1,2,3,3,3 heptafluoropropane ("HFA-227ea") that have been identified as safe for use in pressurized metered dose inhalers.

Medicinal aerosol formulations are generally of the solution or suspension type. Each type is composed of at least the medicament and the propellant. The solution type aerosol formulation contains the medicament dissolved or solubilized in the propellant, or a mixture of propellant and cosolvent. The suspension type aerosol formulation contains the medicament in the form of particles which are dispersed in the propellant. The suspension type aerosol formulations usually contains a surfactant, and can also include a cosolvent. Conventional Budesonide aerosol formulations are of the suspension type. Conventional Formoterol aerosol formulations are of the solution and suspension type.

U.S. Patent No. 5,736,124 (Akehurst) discloses a suspension type aerosol formulation in which the medicament is in the form of particles dispersed in a cosolvent. The cosolvent is present in an amount less than 5% by weight to avoid dissolving the medicament (column 4, lines 13-24).

Published International Application No. WO 98/05302 discloses a suspension type aerosol formulation in which the medicament is in the form of particles dispersed in a cosolvent. The cosolvent can be present in amount of from 6 to 25% by weight. However, this application teaches

that the medicament and cosolvent selected should be such that the medicament is not dissolved in the cosolvent and the particulate shape of the medicament is retained.

Ethanol has been used as a cosolvent. However, previous teachings such as European Patent No. EP 0 616525 have taught away from using concentrations of ethanol greater than 5% in solution aerosol formulations for ß-agonists.

Each of the drugs Budesonide and Formoterol has proven difficult to formulate into conventional aerosol compositions. Such formulations have exhibited short shelf-lives and require refrigeration. Refrigeration is undesirable because many patients are required to carry the aerosol canisters on their persons. There remains, therefore, an important need for aerosol formulations containing Budesonide and Formoterol that remain chemically and physically stable during storage at ambient conditions of temperature and humidity.

SUMMARY OF THE INVENTION

An objective of the present invention is to provide a pressurized metered dose inhaler containing a stable solution formulation of Budesonide and Formoterol which does not require the use of refrigeration.

Another objective of the present invention is to provide a stable solution formulation of Budesonide and Formoterol that is suitable for use as an aerosol, which does not require the use of refrigeration.

The above objectives and other objectives are surprisingly achieved by the following. The present invention provides a novel pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation formulated from a composition comprising:

Budesonide;

Formoterol;

at least one fluoroalkane propellant; and

a cosolvent present in an amount that dissolves or solubilizes the Budesonide and Formoterol in the mixture of cosolvent and propellant.

The present invention also provides a novel solution aerosol

formulation formulated from a composition comprising:

Budesonide;

Formoterol;

at least one fluoroalkane propellant; and

a cosolvent present in an amount that dissolves or solubilizes the Budesonide and Formoterol in the mixture of cosolvent and propellant.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

It has been unexpectedly discovered that chemically and physically stable aerosol formulations containing a mixture of Budesonide and Formoterol can be formulated utilizing high concentrations of cosolvent in which the mixture of Budesonide and Formoterol is dissolved or solubilized in the mixture of cosolvent and propellant. Budesonide and Formoterol aerosol formulations can be formed according to the present invention which exhibit enhanced stability under elevated temperatures (40☜C), thus requiring no refrigeration. The term "Formoterol" is hereinafter understood to mean the base form of Formoterol as well as the weak acid form of Formoterol, unless stated otherwise. A preferred weak acid form of Formoterol is Formoterol fumarate. When Formoterol fumarate is utilized in combination with Budesonide, the amount is usually from about 0.01 to about 0.5% by weight, preferably about 0.01 to about 0.1% by weight. All weight percents are based on the total weight of the formulation unless stated otherwise.

The amount of Budesonide utilized in the present solution type aerosol formulations is usually from about 0.01 to about 1% by weight, preferably about 0.05 to about 0.5% by weight, and most preferably about 0.3% by weight, based on the total weight of the aerosol formulation.

Any cosolvent that is suitable for inhalation and capable of dissolving or solubilizing the mixture of Budesonide and Formoterol in the mixture of cosolvent and propellant can be used. Examples of suitable cosolvents include alcohols, ethers, hydrocarbons, and perfluorocarbons. Preferably, the cosolvent is a short chain polar alcohol. More preferably, the cosolvent is an aliphatic alcohol having from one to six carbon atoms, such as ethanol or isopropanol. The most preferred cosolvent is ethanol. Examples of suitable hydrocarbons include n-butane, isobutane, pentane,

neopentane and isopentanes. Examples of suitable ethers include dimethyl ether and diethyl ether. Examples of suitable perfluorocarbons include perfluoropropane, perfluorobutane, perfluorocyclobutane, and perfluoropentane.

When ethanol is utilized as the cosolvent, the cosolvent is usually present in an amount of from about 6% to about 40% by weight, based on the total weight of the aerosol formulation. The ethanol should be present in an amount which fully dissolves or solubilizes Budesonide and Formoterol in the mixture of ethanol and propellant. Preferably, ethanol is present in amount sufficient to fully maintain the Budesonide and Formoterol in solution at freezing temperatures, such as 0°C. In general, as the temperature is decreased, the solubility of Budesonide and Formoterol in ethanol is decreased. Therefore, an excess of ethanol over the amount required to fully dissolve or solubilize Budesonide and Formoterol at ambient or room temperature is preferred. In this regard, ethanol is preferably present in an amount of at least 10% by weight, more preferably at least 15% by weight, even more preferably at least 20% by weight, and most preferably at least 25% by weight. Based on the disclosure provided herein, one skilled in the art will recognize that lower concentrations of medicament usually require lower concentrations of cosolvent, and vice versa, in order to form a stable solution. Furthermore, one skilled in the art will recognize that the type of propellant utilized can also affect the amount of ethanol required to fully dissolve or solubilize Budesonide and Formoterol in the mixture of ethanol and propellant. In general, the greater the polarity of the propellant the less ethanol required to fully dissolve or solubilize Budesonide and Formoterol.

For example, when HFA-134a is utilized as the propellant, the amount of ethanol is preferably from about 10 to about 30% by weight. When HFA-227ea is utilized, preferred amounts of ethanol are from about 6 to about 20% by weight.

Any fluoroalkane propellant that is suitable for inhalation can be used. Examples of suitable fluoroalkanes include HFA-134a, HFA-227ea, HFA-125 (pentafluoroethane), HFA-152a (1,1-difluoroethane), and HFA-32 (difluoromethane). Hydrocarbon and/or aliphatic gases may be added to modify propellant characteristics as required. Preferably, the aerosol formulation is substantially free of chlorofluorocarbons. However, if

desired chlorofluorocarbons can be utilized. Preferably, the fluoroalkane is 1,1,1,2-tetrafluoroethane (HFA-134a) or 1,1,1,2,3,3,3-heptafluoropropane (HFA-227ea). Most preferably, only a single fluoroalkane is utilized as the propellant.

The propellant is usually present in an amount of from about 60% to about 94% by weight, preferably from about 70 to about 90% by weight, based on the total weight of the aerosol formulation.

A preferred aerosol formulation comprises HFA-134a or HFA-227ea in an amount less than about 90% by weight, ethanol in an amount of at least about 10% by weight, Budesonide in an amount of from about 0.05 to 0.5% by weight, and Formoterol fumarate in an amount of from about 0.01 to about 0.1 % by weight. A particularly preferred aerosol formulation comprises about 75 % by weight of HFA-134a, about 25 % by weight of ethanol, about 0.3 % by weight of Budesonide, and about 0.01% by weight of Formoterol fumarate. The aerosol formulation is preferably free of surfactants.

Pressurized metered dose inhalers are now well known in the art. Any pressurized metered dose inhaler that is suitable for application of medicaments to the lungs or nose of a patient can be used. Pressurized metered dose inhalers usually are equipped with an actuator having a spray orifice diameter of about 460μm. However, with the higher concentrations of solvent employed in the present invention, it may be desirable that the solvent evaporates as soon as possible after inhalation. This can be achieved by reducing particle size by reducing the spray orifice diameter, for example, to 250μm, in combination with using solvent concentrations greater than about 10% by weight. Based on the disclosure provided herein, one skilled in the art will be able to adjust the component composition to deliver a desired dose for the selected metered valve, without undue experimentation. For example, the composition may be altered to adjust the vapor pressure of the formulation. The aerosol formulation and metering valve are usually selected to provide a therapeutically effective amount of the Budesonide and Formoterol per activation. An example of a therapeutically effective amount of Budesonide is about 50 to about 400 ☞g per activation, preferably about 150 to about 250 ☞g per activation. An example of a therapeutically effective amount of Formoterol fumarate when used in combination with

Budesonide has been found to be about 1 to about 50 ☞g per activation, preferably about 5 to about 25 ☞g per activation.

The pressurized metered dose inhaler can be formed by any suitable method. For example, the selected amount of Budesonide and Formoterol can be weighed and inserted into a suitable container, such as a plastic coated glass bottle or aluminum canister. The cosolvent can then be weighed and added to the container. Once all of the non-gaseous components have been added to the container, the metered valve can be crimped on to seal the container. Then, the desired amount of propellant can be added to the container through the metered valve. The Budesonide and Formoterol can be dissolved or solubilized into the mixture of cosolvent and propellant by agitating the formulation, such as by sonication. About 5 minutes of sonication has been found to be suitable to fully dissolve or solubilize a formulation having a total weight of about 13 grams.

The present invention will now be explained with reference to the following non-limiting examples.

Examples 1- 4

Four solution aerosols compositions according to the present invention were formulated by combining the components shown in Tables I and II, using the following steps:

1. Weighing the cosolvent into a plastic coated glass bottle or an aluminum canister.
2. Adding the weighed medicaments.
3. Crimping a valve upon the bottle or canister.
4. Adding a known amount of propellant through the valve into the bottle or canister.
5. Sonicating the formulation for about 5 minutes.

The formulations were tested using the following three very well known methods and the Pharmacopeia Forum, vol. 22, no. 6 standards:

(1) Andersen Multistage Cascade Impactor;

(2) Single Stage Liquid Impinger; and

(3) Unit Spray.

Table III discloses the test results of the Example 1 and 2 formulations using the Unit Spray analysis. These results indicate reproducible dosing throughout the product's life. No significant degradation of medicaments or impurities were observed during these tests.

Table VI discloses the test results of the Examples 3 and 4 formulations using a Unit Spray Analysis, in which the formulations were stored in an oven at 40☜C for 5 days. The test results in Table VI demonstrate that the Budesonide and Formoterol aerosol formulations according to the present invention are remarkably stable at elevated temperatures and therefore do not require refrigeration. The test results also demonstrate that about 10% of the medicament was retained on the actuator and about 90% of the medicament was dispensed to the dose tube, which represents that the composition is acceptable for use as an aerosol formulation.

Table V discloses the test results of the Example 3 formulation using an Andersen Multistage Cascade Impactor for the beginning, middle and end of can. These test results demonstrate that the solution formulation according to the present invention is suitable for application to the lungs. The stages 2 through F represent medicament that is capable of reaching the lungs from a conventional applicator. A total medicament amount of about 30% for stages 2 through F is considered good. As can be seen from Table V, the beginning and middle of the can for both Formoterol and Budesonide each exhibited a total medicament amount of about 30% for the stages 2 through F.

Table I

	Component	Weight (g)	%
Example 1	Formoterol	0.001517	0.011
	Budesonide	0.03855	0.28
	Ethanol	2.22	16.5
	HFA-134a	11.207	83.2
Example 2	Formoterol	0.001194	0.0099
	Budesonide	0.03910	0.32
	Ethanol	2.280	18.8
	HFA-134a	9.7904	80.8

Table II

Example 3	Formoterol	0.0012396	0.0090
	Budesonide	0.04322	0.31
	Ethanol	3.4026	24.7
	HFA-134a	10.3515	75.0
Example 4	Formoterol	0.001293	0.0096
	Budesonide	0.04287	0.32
	Ethanol	3.49130	25.9
	HFA-134a	9.97050	76.3

Table III

Test	**Example 1 (Stored in Oven for 9 days)**			**Example 2 (Room Temperature)**		
Unit Spray Content	Shot numbers	Formoterol (%)	Budesonide (%)	Shot numbers	Formoterol (%)	Budesonide (%)
Test 1	1-20	71	92	1-20	83	96
Test 2	21-40	74	95	21-40	87	95
Test 3	41-60	76	99	41-60	88	98
Test 4	61-80	77	99	61-80	87	98
Test 5	81-100	76	94	81-100	88	94
Test 6	101-120	75	95	101-120	88	97
Test 7	121-140	79	97	121-140	90	100
Test 8	141-160	80	100	141-160	99	104
	Average	76	96	Average	89	98

Table IV

Test	Example 3			Example 4		
Unit Spray Content	Shot numbers	Formoterol (%)	Budesonide (%)	Shot numbers	Formoterol (%)	Budesonide (%)
Test 1	3-4	74	94	3-4	82	88
Test 2	5-6	76	95	5-6	87	92
Test 3	27-28	83	91		na	na
Test 4	29-30	84	92		na	na
Test 5	111-112	87	96		na	na
Test 6	113-114	87	97		na	na
	Average	82	94	Average	85	90

Table V

	Formoterol						Budesonide					
	(Beginning)		(Middle)		(End)		(Beginning)		(Middle)		(End)	
	Amt.(μg)	Amt.(%)	Amt.(μg)	Amt.(%)	Amt.(μg)	Amt.(%)	Amt.(μg)	Amt.(%)	Amt.(μg)	Amt.(%)	Amt.(μg)	Amt.(%)
Actuator	10.5	9.6	7.84	7.1	17.2	16.0	398.4	9.8	290.6	6.90	659.8	15.0
Valve	0.6	0.5	0.63	0.6	0.7	0.6	22.7	0.6	16.1	0.38	0.0	0.0
Induction Port	54.8	50.0	61.4	55.8	58.1	53.9	2162.0	53.3	2364.7	56.11	2449.1	55.5
Stage 0	6.2	5.6	5.2	4.7	7.5	7.0	235.8	5.8	213.3	5.06	324.3	7.4
Stage 1	1.9	1.7	1.5	1.4	1.2	1.1	75.9	1.9	66.7	1.58	90.0	2.0
Stage 2	0.7	0.7	0.9	0.8	0.4	0.4	19.1	0.5	25.9	0.62	22.5	0.5
Stage 3	1.5	1.4	2.3	2.1	1.0	1.0	55.6	1.4	89.5	2.12	52.7	1.2
Stage 4	7.2	6.6	7.3	6.6	5.5	5.1	271.5	6.7	281.7	6.68	226.0	5.1
Stage 5	15.4	14.0	13.5	12.3	8.2	7.6	443.1	10.9	498.5	11.83	235.8	5.4
Stage 6	5.6	5.1	4.7	4.3	4.4	4.1	175.8	4.3	178.2	4.23	179.6	4.1
Stage 7	2.8	2.5	2.0	1.8	1.6	1.5	95.5	2.4	81.3	1.93	85.4	1.9
Stage F	2.5	2.3	2.8	2.5	1.9	1.8	102.7	2.5	108.1	2.56	85.4	1.9
Total Drug	109.5	100	110	100	107.8	100	4058.1	100	4214.6	100	4410.7	100
No Shots	20		20		20		20		20		20	
Avg. Shot Weight	68.23		68.23		68.28		68.23		68.23		68.28	
Actual Dose Delivered (μg/ actuation)	5.47		5.51		5.39		202.90		210.73		220.53	
Material Balance (%)	89		90		88		95		99		103	
MMAD (microns)	2.0		2.0		2.4		2.1		2.0		2.8	
GSD	2.6		2.6		3.0		2.9		2.7		3.5	
Fine Particle Dose (μg)	36		34		23		1163		1263		887	
Fine Particle Fraction (%)	37		33		26		32		32		24	

While the claimed invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one of ordinary skill in the art that various changes and modifications can be made to the claimed invention without departing from the spirit and scope thereof.

CLAIMS:

1. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation formulated from a composition comprising:
   Budesonide;
   Formoterol;
   at least one fluoroalkane propellant; and
   a cosolvent present in an amount that dissolves or solubilizes said Budesonide and Formoterol in the mixture of cosolvent and propellant.

2. A pressurized metered dose inhaler according to claim 1, wherein said cosolvent comprises ethanol.

3. A pressurized metered dose inhaler according to claim 2, wherein said ethanol is present in an amount of at least 10% by weight.

4. A pressurized metered dose inhaler according to claim 2, wherein said ethanol is present in an amount of at least 15% by weight.

5. A pressurized metered dose inhaler according to claim 2, wherein said ethanol is present in an amount of at least 20% by weight.

6. A pressurized metered dose inhaler according to claim 2, wherein said ethanol is present in an amount of at least 25% by weight.

7. A pressurized metered dose inhaler according to claim 1, wherein said formulation is free of a surfactant.

8. A pressurized metered dose inhaler according to claim 1, wherein said propellant comprises 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane.

9. A pressurized metered dose inhaler according to claim 1, wherein said Budesonide is present in an amount of from about 0.01 to about 1% by weight and said Formoterol is present in an amount of from about 0.01 to about 0.5% by weight, based on the total weight of the composition.

10. A pressurized metered dose inhaler according to claim 1, wherein said formulation is substantially free of chlorofluorocarbons.

11. A pressurized metered dose inhaler according to claim 1, wherein said propellant is present in an amount of from about 70 to about 94% by weight.

12. A pressurized metered dose inhaler according to claim 1, wherein said cosolvent is present in an amount sufficient to maintain said Budesonide and Formoterol in solution at 0°C.

13. A pressurized metered dose inhaler according to claim 1, wherein said cosolvent comprises an aliphatic alcohol having from 1 to about 6 carbon atoms.

14. A pressurized metered dose inhaler according to claim 1, wherein said Budesonide is present in an amount of about 0.05 to about 0.5% by weight, said Formoterol is present in an amount of about 0.01 to about 0.1% by weight, said cosolvent comprises ethanol in an amount of about 10 to about 40% by weight, and said propellant is present in an amount of from about 60% to about 90% by weight, all weights based on the total weight of said aerosol formulation.

15. A pressurized metered dose inhaler according to claim 1, wherein said aerosol formulation is adapted to be stable under conditions up to about 40°C and about 75% relative humidity for at least about four weeks.

16. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation formulated from a composition comprising:

Budesonide;

Formoterol;

1,1,1,2-tetrafluoroethane as a propellant; and

at least about 10% ethanol, wherein the ethanol is present in an amount that dissolves or solubilizes said Budesonide and Formoterol in the mixture of 1,1,1,2-tetrafluoroethane and propellant.

17. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation formulated from a composition comprising:

Budesonide;

Formoterol;

1,1,1,2,3,3,3-heptafluoropropane as a propellant; and

at least about 10% ethanol, wherein the ethanol is present in an amount that dissolves or solubilizes said Budesonide and Formoterol in the mixture of 1,1,1,2,3,3,3-heptafluoropropane and propellant.

18. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

Budesonide;

Formoterol;

at least one fluoroalkane propellant; and

a cosolvent present in an amount that dissolves or solubilizes said Budesonide and Formoterol in the mixture of cosolvent and propellant.

19. A solution aerosol formulation according to claim 18, wherein said cosolvent comprises ethanol.

20. A solution aerosol formulation according to claim 19, wherein said ethanol is present in an amount of at least 10% by weight.

21. A solution aerosol formulation according to claim 19, wherein said ethanol is present in an amount of at least 15% by weight.

22. A solution aerosol formulation according to claim 19, wherein said ethanol is present in an amount of at least 20% by weight.

23. A solution aerosol formulation according to claim 19, wherein said ethanol is present in an amount of at least 25% by weight.

24. A solution aerosol formulation according to claim 18, wherein said formulation is free of a surfactant.

25. A solution aerosol formulation according to claim 18, wherein said propellant comprises 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane.

26. A solution aerosol formulation according to claim 18, wherein said Budesonide is present in an amount of from about 0.01 to about 1% by weight, based on the total weight of the composition and said Formoterol is present in an amount of about 0.01 to about 0.5% by weight.

27. A solution aerosol formulation according to claim 18, wherein said formulation is substantially free of chlorofluorocarbons.

28. A solution aerosol formulation according to claim 18, wherein said propellant is present in an amount of from about 70 to about 94% by weight.

29. A solution aerosol formulation according to claim 18, wherein said cosolvent is present in an amount sufficient to maintain said Budesonide and Formoterol in solution at 0°C.

30. A solution aerosol formulation according to claim 18, wherein said cosolvent comprises an aliphatic alcohol having from 1 to about 6 carbon atoms.

31. A solution aerosol formulation according to claim 18, wherein said Budesonide is present in an amount of about 0.05 to about 0.5 % by weight, said Formoterol is present in an amount of about 0.01 to about 0.1% by weight, said cosolvent comprises ethanol in an amount of about 10 to about 40% by weight, and said propellant is present in an amount of from about 60% to about 90% by weight, all weights based on the total weight of said aerosol formulation.

32. A solution aerosol formulation according to claim 18, wherein said aerosol formulation is adapted to be stable under conditions up to about 40°C and about 75% relative humidity for at least about four weeks.

33. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

Budesonide;

Formoterol fumarate;

1,1,1,2-tetrafluoroethane as a propellant; and

at least about 10% ethanol, wherein the ethanol is present in an amount that dissolves or solubilizes said Budesonide and Formoterol fumarate in the mixture of 1,1,1,2-tetrafluoroethane and propellant.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 31/165, 31/58, 9/00, 9/12

A3

(11) International Publication Number: **WO 00/35441**

(43) International Publication Date: 22 June 2000 (22.06.00)

(21) International Application Number: PCT/US99/30163

(22) International Filing Date: 17 December 1999 (17.12.99)

(30) Priority Data:
09/215,280 18 December 1998 (18.12.98) US

(71) Applicant: BAKER NORTON PHARMACEUTICALS, INC. [US/US]; 4400 Biscayne Boulevard, Miami, FL 33137 (US).

(72) Inventors: BLONDINO, Frank, E.; 6237 Rose Terrace, Plantation, FL 33317 (US). BRUCATO, Michael; 9801 N.W. 1st Avenue, Miami Shores, FL 33150 (US). BUENAFE, Maria, W.; 110 Southshore Drive #3–C, Miami Beach, FL 33141 (US). CAVANAUGH, Kelly, A.; 27421 SW, 154th Avenue, Homstead, FL 33032 (US).

(74) Agents: LEVI–MINZI, Simona, A. et al.; Baker Norton Pharmaceuticals, Inc., 4400 Biscayne Boulevard, Miami, FL 33137 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report:
26 October 2000 (26.10.00)

(54) Title: PHARMACEUTICAL AEROSOL FORMULATIONS CONTAINING FLUOROALKANES, BUDESONIDE AND FORMOTEROL

(57) Abstract

Provided is a solution aerosol formulation adapted for use in a pressurized aerosol container. The aerosol formulation is formulated from a composition containing Budesonide, Formoterol at least one fluoroalkane propellant, and a cosolvent present in an amount that dissolves or solubilizes the Budesonide and Formoterol in the mixture of cosolvent and propellant.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/30163

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/165 A61K31/58 A61K9/00 A61K9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 15280 A (ASTRA) 16 April 1998 (1998-04-16) claims page 5, line 7 - line 18	1,2, 7-11,13, 18,19, 24-28,30
A	WO 93 11773 A (ASTRA) 24 June 1993 (1993-06-24) claims page 6, line 17 - line 20 page 6, line 31 - line 36 page 7, line 15 - line 28	1-33

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 July 2000	20/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/30163

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 15182 A (ASTRA) 1 April 1999 (1999-04-01) claims page 3, line 12 - line 17 page 6, line 1 - line 15	1,2, 7-11,13, 18,19, 24-28,30
X,P	WO 99 64014 A (ASTRA) 16 December 1999 (1999-12-16) claims page 6, line 19 - line 30	1,2, 7-11,13, 18,19, 24-28,30

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inc. national Application No
PCT/US 99/30163

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9815280 A	16-04-1998	AU 715319 B	20-01-2000
		AU 4578297 A	05-05-1998
		BR 9706822 A	23-03-1999
		CA 2239308 A	16-04-1998
		CZ 9801761 A	16-09-1998
		EP 0871450 A	21-10-1998
		HU 9901674 A	28-09-1999
		JP 2000502365 T	29-02-2000
		NO 982414 A	27-05-1998
		PL 327037 A	09-11-1998
		SK 75198 A	04-11-1998
WO 9311773 A	24-06-1993	AU 673660 B	21-11-1996
		AU 3085892 A	19-07-1993
		CA 2123909 A	24-06-1993
		CZ 9401434 A	15-12-1994
		EP 0613371 A	07-09-1994
		HR 921445 A	31-12-1994
		HU 75156 A	28-04-1997
		JP 7502036 T	02-03-1995
		NO 942116 A	07-06-1994
		NZ 246050 A	21-12-1995
		SG 48301 A	17-04-1998
		SI 9200403 A	30-06-1993
		SK 73394 A	08-03-1995
		US 5674860 A	07-10-1997
		US 5972919 A	26-10-1999
WO 9915182 A	01-04-1999	AU 9192898 A	12-04-1999
		EP 1014993 A	05-07-2000
		NO 20001401 A	17-03-2000
		ZA 9808516 A	19-03-1999
WO 9964014 A	16-12-1999	AU 4671099 A	30-12-1999